II. REMARKS

Claims 4 to 22 are pending. Claims 4 to 15 are under examination.

Applicants wish to thank the Examiner for the courtesy of an interview a few months ago, which was found to be very helpful.

A. Regarding the amendments.

Claims 4 and 10 have been amended herein to recite a polynucleotide fragment of a polynucleotide sequence encoding heparanase protein (SEQ ID NO:3), the sequence having heparanase activity. As explained by the Examiner in the last Office Action, U.S Patent No. 5,968,822 (hereinafter "the '822 patent), from which the subject application claims priority, discloses that the invention encompasses polynucleotide fragments that include any part of the heparanase gene, which encodes a polypeptide having heparanase activity.

In addition, Applicants wish to point out that the '822 patent also states: "The invention is also directed at providing a single stranded polynucleotide fragment which includes a polynucleotide sequence complementary to at least a portion of a polynucleotide strand encoding a polypeptide having heparanase catalytic activity as described above. The term "complementary" as used herein refers to the ability of base pairing. The single stranded polynucleotide fragment may be DNA or RNA or even include nucleotide analogs (e.g., thioated nucleotides), it may be a synthetic oligonucleotide or manufactured by transduced host cells, it may be of any desired length which still provides specific base pairing (e.g., 8 or 10, preferably more, nucleotides long) and it may include mismatches that do not hamper base pairing." (Column 12, lines 49-62).

Moreover, the subject application discloses that "The present invention is of heparanase specific molecular probes which can be used in research and medical applications. Specifically, the present invention can be used for the detection and monitoring of malignancies, metastasis and other, non-malignant conditions, efficiency of therapeutic treatments, targeted drug delivery and therapy, using heparanase specific molecular probes, such as anti-heparanase antibodies (both poly- and monoclonal) and heparanase gene (hpa) derived nucleic acids, including, but not limited to, **PCR primers**, antisense oligonucleotide probes, antisense RNA probes, DNA probes and the like. Page 20, lines 9-16 (emphasis added).

In addition, the subject application discloses that "according to another aspect of the present invention there is provided a method of detecting the presence, absence or level of **heparanase transcripts** in a biological sample. The method comprises the following steps. First, messenger RNA (e.g., as a component of total RNA) is extracted from the biological sample, thereby a plurality of messenger RNAs are obtained. Second, the plurality of messenger RNAs are reverse transcribed into a plurality of complementary DNAs. Third, **the plurality of complementary DNAs are contacted with a pair of heparanase specific polymerase chain reaction (PCR) primers**, nucleoside triphosphates and a thermostable DNA polymerase (e.g., Thermophilus aquaticus DNA polymerase, native or recombinant) and a polymerase chain reaction is performed by temperature cycling, as well known in the art. Finally, the presence, absence or level of the polymerase chain reaction product is detected, e.g., by gel electrophoresis, by monitoring the incorporation of a detectable moiety into the product or any other applicable way, all as well known in the art. Page 23, line 20 to page 24, line 2 (emphasis added).

It is clear from the subject application, that the DNAs directing the PCR amplification need not be amplifying the entire heparanase gene. Rather, these DNAs can amplify a fragment of the gene. By amplifying a fragment, the process can be more efficient and quicker.

For example, one of the sense DNAs actually used for amplification was SEQ ID NO:6 (page 30, lines 11-12). SEQ ID NO:6 binds to nucleotides 372-394 of the full heparanase DNA (SEQ ID NO:1; see page 1 of sequence listing), which corresponds with amino acid 104 of SEQ ID NO:3. Thus, the PCR directed by SEQ ID NO:6 results in amplification of merely a fragment of the heparanase DNA, corresponding to a fragment of the heparanase protein. This was sufficient to evaluate the expression of the heparanase gene by various cell types. (See Table 1 at page 36).

In view of the disclosure of the subject application and the '822 patent, Applicants respectfully submit that no issue of new matter is raised by the amendments made herein.

B. Regarding the written description rejection.

Claims 4 to 15 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement. Specifically, the Action objected to the terms "to at least a portion of SEQ ID NO: 3" and "wherein said polynucleotide sequence is the most prevalent polynucleotide product of said PCR amplification." In a second written description rejection, the Action objects to the term "at least 90% homologous to at least a portion of SEQ ID NO:3." Applicants respectfully traverse these rejections.

Because these terms have been deleted from the claims, Applicants request that these rejections be withdrawn.

Applicants wish to point out that claims 4 and 10 (and all claims dependent thereon) have now been amended to recite a polynucleotide fragment of a

polynucleotide sequence encoding heparanase protein (SEQ ID NO:3), the sequence having heparanase activity. As explained by the Examiner in the last Office Action, the '822 patent, from which the subject application claims priority, discloses that the invention encompasses polynucleotide fragments that include any part of the heparanase gene, which encodes a polypeptide having heparanase activity.

In addition, Applicants wish to point out that the '822 patent also states: "The invention is also directed at providing a single stranded polynucleotide fragment which includes a polynucleotide sequence complementary to at least a portion of a polynucleotide strand encoding a polypeptide having heparanase catalytic activity as described above. The term "complementary" as used herein refers to the ability of base pairing. The single stranded polynucleotide fragment may be DNA or RNA or even include nucleotide analogs (e.g., thioated nucleotides), it may be a synthetic oligonucleotide or manufactured by transduced host cells, it may be of any desired length which still provides specific base pairing (e.g., 8 or 10, preferably more, nucleotides long) and it may include mismatches that do not hamper base pairing." (Column 12, lines 49-62).

Moreover, the subject application discloses that "The present invention is of heparanase specific molecular probes which can be used in research and medical applications. Specifically, the present invention can be used for the detection and monitoring of malignancies, metastasis and other, non-malignant conditions, efficiency of therapeutic treatments, targeted drug delivery and therapy, using heparanase specific molecular probes, such as anti-heparanase antibodies (both poly- and monoclonal) and heparanase gene (hpa) derived nucleic acids, including, but not limited to, **PCR primers**, antisense oligonucleotide probes, antisense RNA probes, DNA probes and the like. Page 20, lines 9-16 (emphasis added).

In addition, the subject application discloses that "according to another aspect of the present invention there is provided a method of detecting the presence, absence or level of **heparanase transcripts** in a biological sample. The method comprises

the following steps. First, messenger RNA (e.g., as a component of total RNA) is extracted from the biological sample, thereby a plurality of messenger RNAs are obtained. Second, the plurality of messenger RNAs are reverse transcribed into a plurality of complementary DNAs. Third, **the plurality of complementary DNAs are contacted with a pair of heparanase specific polymerase chain reaction (PCR) primers**, nucleoside triphosphates and a thermostable DNA polymerase (e.g., Thermophilus aquaticus DNA polymerase, native or recombinant) and a polymerase chain reaction is performed by temperature cycling, as well known in the art. Finally, the presence, absence or level of the polymerase chain reaction product is detected, e.g., by gel electrophoresis, by monitoring the incorporation of a detectable moiety into the product or any other applicable way, all as well known in the art. Page 23, line 20 to page 24, line 2 (emphasis added).

It is clear from the subject application, that the DNAs directing the PCR amplification need not be amplifying the entire heparanase gene. Rather, these DNAs can amplify a fragment of the gene. By amplifying a fragment, the process can be more efficient and quicker.

For example, one of the sense DNAs actually used for amplification was SEQ ID NO:6 (page 30, lines 11-12). SEQ ID NO:6 binds to nucleotides 372-394 of the full heparanase DNA (SEQ ID NO:1; see page 1 of sequence listing), which corresponds with amino acid 104 of SEQ ID NO:3. Thus, the PCR directed by SEQ ID NO:6 results in amplification of merely a fragment of the heparanase DNA, corresponding to a fragment of the heparanase protein. This was sufficient to evaluate the expression of the heparanase gene by various cell types. (See Table 1 at page 36).

Thus, in view of the disclosure of the subject application and the '822 patent, no issue of new matter is raised by the amendments made herein. Accordingly, Applicants respectfully request that this rejection be withdrawn.

C. Regarding the enablement rejection.

Claims 4, 7 to 10, 12, 14 and 15 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly not enabled. Specifically, the Action object to the scope of the claims, given the recited phrase "at least 90% homologous" to SEQ ID NO: 3. Further, the Action alleges that, given this breadth, there is a lack of guidance and therefore extended experimentation required to determine which sequences and/or substitutions would be required to retain functional activity. Applicants respectfully traverse the rejection.

Although Applicants disagree with the Action's allegations, to promote prosecution of the subject application, the claims have now been amended by deleting any homology percentage to SEQ ID NO: 3. Thus, the claims are limited to known sequences. Accordingly, Applicants respectfully submit that the skilled artisan, who is well versed in PCR methodology, as described in the subject application and as known in the art, would know how to carry out the invention, as presently claimed, without undue experimentation, and as shown using the examples described in the '822 patent and the subject application, as discussed above.

In view of the amendments made herein, Applicants respectfully request that this rejection be withdrawn.

D. Regarding the prior art rejections.

The Action has made three anticipation rejections and three obviousness rejection based on deeming the priority date of the subject application as the filing date of the subject application (October 2, 2003). The Action makes this determination because the prior claim limitations are alleged not to be supported by the parent applications. Applicants respectfully traverse these rejections.

In response, the referred to "claim limitations" alleged not to be supported by the subject application have been deleted herein. Accordingly, the priority date of the subject application is no later than May 1, 1998.

The first anticipation rejection (paragraph 10 of the Action) is based on a reference published March 11, 1999. Because the priority date of the subject application predates this reference, this rejection must fail.

The second anticipation rejection (paragraph 11 of the Action) is based on a reference published November 11, 1999. Because the priority date of the subject application predates this reference, this rejection must also fail.

The third anticipation rejection (paragraph 12 of the Action) is based on a reference published August 1, 2002. Because the priority date of the subject application predates this reference, this rejection must also fail.

The first obviousness rejection (paragraph 14 of the Action) is based, in part, on a reference published March 11, 1999. Because the priority date of the subject application predates this reference, this rejection must fail.

The second obviousness rejection (paragraph 15 of the Action) is based, in part, on a reference published August 1, 2002. Because the priority date of the subject application predates this reference, this rejection must also fail.

The third obviousness rejection (paragraph 16 of the Action) is based, in part, on a reference published November 11, 1999. Because the priority date of the subject application predates this reference, this rejection must also fail.

Accordingly, Applicants respectfully request that all of the prior art rejections be withdrawn.

III. CONCLUSION

All of the issues raised in the Office Action have been addressed and are believed to have been overcome. Accordingly, it is respectfully submitted that all the claims under examination in the subject application are allowable. Therefore Applicants respectfully request a Notice of Allowance to this effect.

Respectfully submitted,

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Martin Moynihan,
Registration No. 40,338

Date: July 12, 2005

Encls.
Request for Continued Examination, with fee
Petition for three-month extension, with fee